In the Specification

Please substitute the following paragraph beginning on page 4, line 33, through to page 5, line 17:

Measuring the percentage modification of RNA:

Due to the polymeric nature of RNA, it is difficult to measure its molecular weight above 100 nucleotides using mass spectrometry because a large amount of RNA degradation occurs during the analytical process. However, RNA (tRNA) up to 142 nucleotides (Nordhoff et al., (1993) Nucleic Acids Res. 21:3347; Gruic-Sovulj et al., (1997) Nucleic Acids Res. 25:1859; Tolson and Nicholson (1998) Nucleic Acids Res. 26:446) and double stranded DNA up to 500 base-pairs (Bai ~~et al.~~ et al., (1995) Rapid Comm. Mass Spectrom. 9:1172; Taranenko et al., (1998) Nucleic Acids Res. 26:2488; Ausdall and Marshall (1998) Anal. Biochem. 256:220) have been measured using MALDI mass spectrometry (for reviews see; Smith (1996) Nat. Biotech. 14:1084; Murray (1996) J. of Mass Spectrom. 31:1203. Phosphate (Schuette et al., (1995) J. Pharm. Biomed. Anal. 13:1195; Sinha et al., (1994) Nucleic Acids Res. 22:3119) and chemically modified oligonucleotides (Potier et al., (1994) Nucleic Acids Res. 22:3895) have also been measured using mass spectrometry.

Please substitute the following paragraph beginning on page 7, line 1:

It will be understood that the 2'-OH modification may inhibit degradation of the polynucleotide. However, by empirically determining the sensitivity of the modified RNA to a range of conditions it ~~will be should be~~ will be/should be possible in most cases to select conditions that are suitable for chain cleavage. For example, it has been found that acetylated RNA is readily cleaved by nuclease Bal 31. Whilst alkali cleaves acetylated RNA it also results in acetyl cleavage so unless the amount of cleaved acetyl groups is measured by mass spectrometry, acetylated nucleotides will not be detected. For example, acid cleavage of the modified polynucleotide can be used for base sensitive modifications, whilst base cleavage can be used for acid sensitive modifications. It will also be understood that other degradation products such as dinucleotides, trinucleotides ~~etc~~ etc. will also be suitable for measuring the percentage modification of the polynucleotide. Whether it is the nucleotide, dinucleotide or larger fragments that are being measured, in each case it is the ratio of the

number of fragments bearing a modification compared with the number of fragments not bearing a modification that provides the percentage modification.

Please substitute the following paragraph beginning on page 8, line 6:

It is now much more common to measure the molecular weight of polynucleotides using electrophoretic separation in polyacrylamide or agarose gels. Detailed descriptions of the preparation, use and handling of electrophoresis gels is described in several publications (Sambrook et al., (1989) Molecular Cloning: A Laboratory Manual, CSH; Jones (1995) Gel Electrophoresis: Nucleic Acids Essential Techniques, Wiley). Denaturing gels are preferred to non-denaturing gels because they reduce conformational effects providing a means to measure the true molecular weight of the linear polynucleotide (Jones (1995) Gel Electrophoresis: Nucleic Acids Essential Techniques, page 47, Wiley). There are a variety of denaturants that can be used such as DMSO (50-90%), glyoxal (10-30%), formaldehyde (3% w/v), formamide (50-98%), heat (60-80°C), methyl mercuric hydroxide (3-5mM), sodium iodoacetate (10mM), 2-pyrrolidone (5%) and urea (6-8mM). It is known that incomplete denaturation of the polynucleotide leads to anomalous migration so that more than one denaturing condition may be required such as 8M urea plus 5% ~~pyrrolidonone~~ pyrrolidone or 8M urea run at 60°C (Rosenblum et al., (1997) Nucleic ~~Acids.~~ Acids Res. 25:3925). Capillary electrophoresis provides an excellent means to carry out such molecular weight determinations and suitable methods have been described for RNA (Engel and Dieguez-Lucena (1993) Nucleic Acids Res. 21:759).

Please substitute the following paragraph beginning on page 16, line 26 through to page 17, line 11:

The hydrophobic substituent typically comprises a substituent, OR, wherein R comprises C_1-C_{36} alkyl; C_1-C_{36} alkenyl; C_1-C_{36} alkynyl; C_1-C_{36} haloalkyl; C_1-C_{36} aminoalkyl; C_1-C_{36} alkoxyalkyl; C_1-C_{36} alkylthioalkyl; C_1-C_{36} alkoxyalkoxyalkyl; C_1-C_{36} haloalkoxyalkyl; C_1-C_{36} aminoalkoxyalkyl; C_6-C_{36} aryl; C_6-C_{36} alkylaryl; C_6-C_{36} arylalkyl; C_6-C_{36} arylalkenyl; C_1-C_{36} alkanoyl; C_1-C_{36} alkenoyl; C_1-C_{36} haloalkenoyl; C_1-C_{36} haloalkanoyl; C_2-C_{36} haloformylalkanoyl; ~~C_1-C_{36}~~ C_1-C_{36} aminoalkanoyl; C_1-C_{36} azidoalkanoyl; C_1-C_{36} carboxyalkanoyl; C_1-C_{36} carboxyalkenoyl; C_1-C_{36}

carboxyalkynoyl; C_1-C_{36} alkylaminoarylalkanoyl; C_1-C_{36} alkoxycarbonyl; C_1-C_{36} alkenyloxycarbonyl; C_1-C_{36} alkylsulfonyl; C_6-C_{36} arylalkanoyl; C_6-C_{36} arylalkenoyl; C_6-C_{36} aryloxyalkanoyl; C_6-C_{36} alkylarylalkanoyl; C_6-C_{36} haloarylalkanoyl; C_6-C_{36} aminoarylalkanoyl; C_1-C_{36} alkylsilanyl; C_1-C_{36} trialkylsilanyl or C_{12}-C_{28} diarylphosphano; or a substituent R', wherein R' comprises C_1-C_{36} alkyl; C_1-C_{36} alkenyl; C_1-C_{36} alkynyl; C_1-C_{36} haloalkyl; C_1-C_{36} aminoalkyl; halo; amino; C_1-C_{36} alkylamino; C_6-C_{36} aryl; C_1-C_{36} alkylaryl or C_1-C_{36} arylalkyl.

Please substitute the following paragraph beginning on page 29, line 19, through to page 30, line 8:

A practical solution to non-specific protein binding to the BCPB beads may be the use of a protein removal step before the addition of the BCPB beads to the sample. For example this may consist of a protein pre-binding step: a serum sample containing the RNA analyte may be added to, or passed through a protein binding surface such as a hydrophobic bead, membrane, filter or other protein capture surface and then the solution containing the deproteinised RNA added to the reactant-solid phase such as BCPB beads. Suitable membranes that are known to capture proteins but not nucleic acids include 0.45 μm pore size IMMOBILON-P (hydrophobic polyvinylidene fluoride, Millipore, US). Alternatively, proteins could be separated from an RNA virus by filtration whereby the proteins but not the virus particles pass through an ultrafiltration membrane with a nominal molecular weight cut-off of ~~30 000 – 100 000~~ 30,000 – 100,000 daltons such as CENTRICON -100, CENTRIPLUS-100 (Amicon, US). Filters with pore sizes above 0.01 μm such as ISOPORE 0.05 μm polycarbonate membranes (Millipore, US) should generally capture most virus particles from blood serum whilst allowing most proteins to pass through. Such collected virus particles could then be added to the reactant-solid phase such as BCPB beads.

Please substitute the following paragraph beginning on page 32, line 31, through to page 33, line 21:

To reiterate, in addition to the preferred BCPB beads, the solid phase could include a particle, a bead, a membrane, ~~agel~~ a gel, a slide or cover slip, an etched silicon surface, a fiber, a filter, a capillary, a tube, a vessel or a multi-vessel plate such as a 96 well plate. It will be apparent that

the use of a solid phase improves handling throughput and accuracy when the RNA immobilization and analysis is automated. In this context, paramagnetic particles are favored for their handling properties. Other preferred solid phases are those which comprise OH groups, e.g. compounds of silicon and oxygen, such as silica particles or a glass. Nucleic acid purification using silica beads is well known and widely practiced both in diagnostic and life science research. Methods of purifying RNA have been described in US patent 5,234,809. Briefly the method involves binding the nucleic acid sample to silica beads in a chaotropic agent such as urea and then washing the beads in a high salt wash before it is eluted into water. The modified RNA used in the present invention has been tested for its ability to bind and be released from silica beads using a silica bead purification kit (Qiagen, Germany) and found to be particularly suited to this type of separation method (see Examples).

Please substitute the following paragraph beginning on page 43, line 1:

60 µl of ethyl-agarose or dodecyl-agarose beads (Sigma, USA) were washed twice in 200 µl of 1.7M ammonium sulphate and collected by centrifugation at 3000g for 5 seconds between washes. 40 µl (20%) of the beads in ~~of~~ 1.7M ammonium sulphate were added to 300ng of isatoic anhydride labeled RNA. It was found that the fluorescent isatoic anhydride modification could be used to monitor binding to the hydrophobic beads under ultra-violet light. On addition to the beads, fluorescent RNA moved from the solvent to the beads within a few seconds demonstrating interaction between the modified RNA and the hydrophobic surface. It was also found that the interaction between the modified RNA and dodecyl-agarose was very strong: 1% TWEEN/1% TRITON X-100, 6M urea, 100% ethanol or loading the sample in a well of an agarose electrophoresis gel and subjecting the bead-RNA complex to 100V for 15min. failed to displace the labelled RNA from the dodecyl-agarose bead whilst 50mM sodium phosphate buffer removed most of the modified RNA from ethyl-agarose beads. An intermediate binding affinity between ethyl and dodecyl was found in the ease of releasing modified RNA from propyl, pentyl and octyl-agarose. Overall, the strength of the hydrophobic interaction is proportional to carbon chain length increasing from ethyl, propyl, pentyl, octyl to dodecyl-agarose.